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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,160	06/24/2003	Bernard Gaudilliere	PC25079A	9990
28880	7590	07/22/2005	EXAMINER	
WARNER-LAMBERT COMPANY 2800 PLYMOUTH RD ANN ARBOR, MI 48105			JOHNSEN, JASON H	
			ART UNIT	PAPER NUMBER
			1623	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/602,160	Applicant(s) GAUDILLIERE ET AL.	
	Examiner Jason H. Johnsen	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 9-20 is/are rejected.
- 7) ☐ Claim(s) 7,8 and 21 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on N/A is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>09/09/04,01/15/04</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1-21 are pending in this application.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I: Claims 1-21(in part), drawn to compounds, compositions, and methods of using formula I, wherein X_1 , X_2 , and X_3 are all CR_3 classified in various subclasses of class 544 depending on the variables.

Group II: Claims 1-21(in part), drawn to compounds, compositions, and methods of using formula I, wherein one of X_1 , X_2 , and X_3 is Nitrogen, and the other two are CR_3 , classified in various subclasses of class 546 depending on the variables.

Group II: Claims 1-21(in part), drawn to compounds, compositions, and methods of using formula I, wherein one of X_1 , X_2 , and X_3 is CR_3 , and the other two are Nitrogen, classified in various subclasses of class 544 depending on the variables.

A telephone call was placed to the attorney of record, Claude Purchase Jr., on March 29, 2005 in which an oral election of Group I without traverse was obtained. Therefore, the claims will be examined commensurate in scope with this election.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 01/15/04 and 09/09/04 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statements.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation. The instant disclosure is not seen to be sufficient to enable the use of compounds of the formula in claim 1 to treat all of the diseases or disorders in claim 16 and 17 without undue experimentation.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;

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- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims are extremely broad due to the large number of diseases and disorders which are potentially mediated by MMP-13 enzyme, including arthritis, rheumatoid arthritis, osteoarthritis, periodontal diseases broadly, multiple sclerosis, cardiac insufficiency broadly, cancer broadly, etc. Applicant has not provided sufficient evidence to support a claim drawn to all of these disorders or diseases.

The nature of the invention

Claim 16 is directed to a method of treating diseases or disorders mediated by MMP-13 enzyme by administering a compound of claim 1, or a racemic form, isomer, N-oxide, or pharmaceutically acceptable salt. Claim 17 are directed to the treatment of specific MMP-13 potentially mediated diseases by administering a compound or composition of claim 1.

The state of the prior art

In the specification on the bottom of page 1 and the top of page 2 applicant indicates that MMP enzymes are involved in the renewal of extracellular matrix tissue by bringing about the destruction of the extracellular matrix tissue, which is compensated for, in a normally conditioned, non diseased physiological environment, by its simultaneous regeneration. Specialized proteins that inhibit MMPs, such as the tissue inhibitors of metalloprotease, control these enzymes. MMP-13 is a collagenase-type MMP that has been shown to mediate pathologies

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of rheumatoid arthritis, osteoarthritis, and breast cancer. However, MMP-13's involvement in other diseases such as psoriasis, periodontal diseases broadly, inflammatory bowel disease, and other types of cancers is still largely theoretical. For example, Salmela et al. authored an article entitled "Inflammation and inflammatory bowel disease", printed in 2002, which taught that many MMPs functions in the gut, including MMP-13, is currently unknown. Furthermore, Salmela et al. taught that MMP-13 was one of a group of MMPs that had no effect on upregulation of stromelysin 2 and macrophage metalloelastase expression associated with mucosal destruction (page 2, under results). Furthermore, Stumpf et al., in "Reduced expression of collagen type 1 and increased expression of matrix metalloproteinases 1 in patients with Crohn's disease," also questioned the involvement of MMP-13 in inflammatory bowel disease (see abstract). Kariniemi et al. ("Metalloelastase and 92 kDa gelatinases as well as their inhibitors TIMP-1 and -3, are expressed in psoriatic lesions), concluded that MMP-13 did not seem to contribute to psoriatic conditions (page 179).

The level of predictability in the art

The instant claimed invention is highly unpredictable. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more

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unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, in the absence of a showing of a nexus between the MMP-13 enzyme inhibiting activity of the compounds of the formula I and the corresponding efficacy of treating a wide variety of disorders listed in claim 17, one of skill in the art is unable to fully predict possible results from the administration of the compound of the formula due to the unpredictability of the art pertaining to diseases and disorders potentially mediated by MMP-13 enzyme.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant provides limited guidance regarding the use of the instant compound in treating a wide variety of disorders each of which have complex etiologies. Applicant provides information on biological activity on pages 28. This data corresponds to MMP-13 inhibitory activity of compounds of formula I. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of treatment of any disorder or disease mediated by MMP-13 enzyme or the broad range of disease found in claim 17.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993). Applicant provides data regarding MMP-13 inhibitory enzyme assays and general

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procedures for these assays. Applicants have correlated a single mechanism to the treatment of diseases and conditions that have complex etiologies. The art does not establish such a link and applicant does not establish a fact based, evidentiary link.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

As discussed above, based on the unpredictable nature of the invention, the state of the prior art, and the extreme breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reason(s):

1. The limitation in claim 1 “and/or wherein when p is greater or equal to 2...” found on page four, line 7 is indefinite because it is unclear, in this context, which p substituent this limitation is referring to. The only definition of p is found on page 1 in the context of the definition of G₁; which states that p represents an integer from 0 to 2 inclusive. Therefore, as stated in the limitation above, p cannot be greater than 2.

3. Claims 2-5, and 9-21 are rejected under 35 U.S.C. 112, second paragraph, because claims that depend from an indefinite claim are also indefinite if they fail to obviate the reason the claim(s) from which they depend are rejected.

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Claim Objections

Claim 7 and claim 8, which depends from claim 7, are objected to because claim 7 depends from itself. Claim 21 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to multiple claims in the alternative. See MPEP § 608.01(n). Accordingly, the claim is not been further treated on the merits.

Claims 1 and 10 contain non-elected subject matter. However, the substantive compounds and compositions found in claims 1-15 and 20 appear to be free of the prior art. The specific substituent G₂ is not taught nor fairly suggested by the prior art. The closest prior art reference, JP 2001131173, does not teach this limitation.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason H. Johnsen** whose telephone number is **571-272-3106**. The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

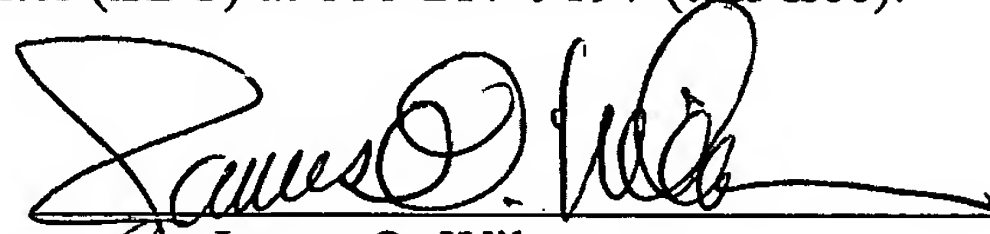
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason H. Johnsen
Patent Examiner
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James O. Wilson
Supervisory Patent Examiner
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